been canceled herein.

Claim 113 has been added in the present application. New claim 113 is fully supported in the specification, and no new matter has been added by way of this amendment.

Applicants note that claims 97 and 98 were not addressed in the present Office Action. Applicants request that the Examiner address the status of these claims in the next Communication.

Rejection of Claims 109-111 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 109-111 as lacking enablement. Specifically, the Examiner argues that the claims are only enabling for methods of providing a protein to a mammal, and not to methods of treating an animal since these claims may be construed to include gene therapy technology.

While Applicants do not necessarily agree with the Examiner's reasoning, in the interest of expediting prosecution, Applicants have canceled claims 109-111 without prejudice to the inclusion of the subject matter contained therein in a later-filed application. Therefore, the rejection of claims 109-111 is rendered moot in view of the cancellation of the claims. Applicants request reconsideration and withdrawal of the rejection.

Rejection of Claims 69-71, 77, 99-108, and 112 under 35 U.S.C. §103(a)

The Examiner has rejected claims 69-71, 99-108, and 112 as being unpatentable in view of either Greenberger et al. (U.S. Pat. No. 5,962,323) or Emerson et al. (U.S. Pat. No. 5,670,351) in combination with any of Caplan (U.S. Pat. No. 5,197,985), Schinstine (U.S. Pat. No. 5,843,431), or Mardon (1987, Cell Tissue Res. 250:157-165).

Preliminarily, Applicants note that the Examiner has rejected claims 69-71, 77, 99-108, and 112 under **35 U.S.C. §102(e)**. In a telephone call on November 5, 2002, the Examiner clarified that these claims were rejected under 35 U.S.C. §103(a) and acknowledged that the recitation of 35 U.S.C. §102(e) within the rejection was a typographical error throughout the Office Action. Accordingly, the Examiner's rejection is addressed herein under §103(a).

In the Examiner's view, Greenberger and Emerson teach a method of using isolated bone marrow stromal cells for implantation and providing a protein of interest to a cell in a mammal, wherein the cells are genetically modified to express the protein of interest. While

the Examiner notes that Greenberger and Emerson do not teach use of a microcarrier, diffusion chamber or microcapsule to deliver cells, the Examiner asserts that the state of the prior art as exemplified by Mardon, Caplan, and Schinstine, was such that these delivery systems were routine and conventional. Thus, the Examiner believes that it would have been obvious to one skilled in the art to combine these references to arrive at the present invention. Applicants believe that the combination of either Greenberger or Emerson with any of the other references does not render these claims prima facie obvious. Thus, Applicants respectfully traverse this rejection.

With respect to Greenberger, Applicants assert that this reference is not prior art since the present application has priority dates of March 28, 1995 and November 13, 1995, and the Greenberger reference has a priority date of December 29, 1995, which is after Applicants' priority dates. However, even if Greenberger were prior art, the reference, combined with any of Mardon, Caplan, or Schinstine does not establish a prima facie case of obviousness as more fully discussed below.

The three-prong test which must be met for a reference or a combination of references to be prima facie obvious has not been satisfied here. The MPEP states that "to establish a prima facie case of obviousness...there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations." MPEP 2142.

As more fully described below, these criteria have not been met here. First, neither Greenberger nor Emerson, combined with any of Caplan, Mardon, or Schinstine, teach or suggest Applicants' invention.

Greenberger teaches a specific set of culture conditions for culturing human and canine bone marrow stromal cells. Greenberger also teaches transfection of canine bone marrow stromal cells in vitro with human growth hormone (hGH). However, Applicants submit that Greenberger does not teach or suggest a composition comprising transfected bone marrow stromal cells to provide a protein in vivo to an animal in need of such protein by providing the transfected bone marrow stromal cell in a container to the animal in need, nor does Greenberger teach a method of using such cells. As openly admitted in Greenberger, the only reason for

transfecting the canine bone marrow stromal cells was to determine whether the cells grown under the described cell culture conditions could in fact be transfected (see column 8, line 52). Clearly, the Greenberger patent is directed toward a specific set of culture conditions for expanding bone marrow stromal cells only. There is no teaching or suggestion for a composition comprising expanded bone marrow stromal cells (and uses therefor) except for "therapeutic uses...in gene therapies" (see column 2, line 15). Certainly, the specification of Greenberger does not provide any guidance as to how one might achieve therapeutic use of the bone marrow stromal cells expanded using the method described. A mere hint such as that thrown out to the reader in column 2, line 15 of Greenberger, that the cells of Greenberger could have therapeutic use, is not enabling and cannot be considered a "teaching or suggestion" within the meaning of 35 U.S.C. §103(a).

Applicants assert that the present invention is far too big a leap from what is taught in the Greenberger specification. One of skill in the art would not have been motivated in any way to combine Greenberger with any of Caplan, Mardon, or Schinstine because one of skill in the art would appreciate that the invention in Greenberger is merely a specific set of culture conditions for expanding bone marrow stromal cells. There is nothing in Greenberger that would compel one of skill in the art to combine what is taught in Greenberger with methods of delivering a cell to an animal in vivo (i.e., the methods of using microcarriers, diffusion chambers, etc.) because Greenberger does not teach or suggest delivery of transfected bone marrow stromal cells to an animal.

The Examiner cited Caplan, Mardon, and Schinstine as indicative of the state of the art with regard to delivery systems for cells (diffusion chambers, microcarriers, etc.), but these references do not in and of themselves render the present invention obvious. Because neither of Caplan, Mardon, or Schinstine (more fully discussed below) do not overcome the deficiencies of Greenberger to (1) teach or suggest compositions and use of transfected bone marrow stromal cells to provide a protein to an animal in need and (2) motivate one of skill in the art to combine any of Caplan, Mardon, or Schinstine with Greenberger, Applicants submit that any combination of these references with Greenberger cannot render the present invention obvious. Therefore, Applicants request reconsideration and withdrawal of this rejection as to the combination of Greenberger and either Caplan, Mardon, or Schinstine.

With respect to Emerson, Applicants have clearly defined the cells of the present

invention in the specification bridging pages 4 and 5 as stromal cells, colony forming cells, marrow stromal cells, adherent cells, or MSCs (i.e., all these terms are synonymous with one another) and refer to the small fraction of cells in the bone marrow that serve as "stem cell"-like precursors of osteocytes, chondrocytes, and adipocytes, and can be isolated from bone marrow by their ability to adhere to plastic. Bone marrow stromal cells are not broadly defined in the specification as stem cells.

Emerson does not teach Applicants' cells. Rather, Emerson teaches hematopoietic stem cells. Further, methods for culturing hematopoietic stem cells, including cell culture conditions, and methods to prepare ex vivo compositions of hematopoietic stem cells are also taught. Emerson does not teach or suggest Applicants' cells, namely, genetically altered bone marrow stromal cells, or the use of Applicants' cells to provide a protein to an animal in need.

Moreover, the Examiner points to columns 7 and 8 of Emerson to support the contention that Emerson teaches use of genetically modified bone marrow stromal cells to treat diseases (paragraph bridging columns 7 and 8). Applicants contend that Emerson does not teach genetically modified bone marrow stromal cells. Emerson merely suggests that genetically modified human stem cells which have been proliferated using the ex vivo culture system of Emerson's invention, but not bone marrow stromal cells, may be useful in treating a wide variety of clinical diseases (see column 7-8); however, Applicants contend that this statement is merely an invitation to experiment with the cell culture conditions taught by Emerson for the cells disclosed in Emerson, which are not Applicants' cells. At column 7, line 65 of Emerson, it is clearly stated that the invention provides "an ex vivo culture system which supports the continuous proliferation of human stem cells to allow the successful insertion of genetic material into the stem cells, resulting in the creation of stably genetically transformed human stem cells." The paragraph in Emerson goes on to state that the genetically modified human stem cells proliferated using the ex vivo culture system can be used to treat clinical diseases (column 8, lines 2-8). Thus, the latter statement is merely satisfying the "utility" requirement for an ex vivo culture system, as set forth in 35 U.S.C. §101. There is no teaching or guidance regarding how to use these stem cells to actually treat clinical diseases.

Emerson does not provide any teaching or suggestion nor are there any experiments or data described in the specification of Emerson to indicate that genetically

modified human bone marrow stromal cells can be used to treat clinical diseases. Emerson does not teach or suggest administration of genetically modified bone marrow stromal cells to an animal in need, nor does Emerson suggest a method for providing a protein to an animal in need by providing genetically modified bone marrow stromal cells in an implantable container from which the protein can diffuse.

Moreover, there are no teachings or suggestions that would motivate one of skill in the art to combine Emerson with any one of Caplan, Schinstine or Mardon to arrive at the present invention. Emerson discloses ex vivo culture systems for different types of cells, including stem cells. One of skill in the art, armed with the disclosure of either Emerson, would not have been motivated to prepare genetically modified bone marrow stromal cells for the purpose of transferring those cells to a container, and implanting the container within an animal in order to provide a protein to the animal.

Further, Applicants point out that the suggestion in Emerson that genetically modified human stem cells can be used to treat a wide variety of clinical diseases is a gene therapy application, which the Examiner strenuously argues in the present Office Action, is an unpredictable area, even at the present time. Therefore, even assuming, *arguendo*, that Emerson could be construed to teach or suggest genetically modified human bone marrow stromal cells, Applicants believe that the Examiner has based his rejection on a reference, which, according to his rejection in the present Office Action, cannot be enabling in the capacity for which it was cited. It is settled law that a reference cannot render obvious a patent claim unless the reference enables the claim. See *In re Paulson*, 30 F.3d 1475, 1478, 31 USPQ 2d 1671, 1673 (Fed. Cir. 1994), wherein it is stated "a reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." Thus, Applicants also contend that Emerson does not enable use of genetically altered bone marrow stromal cells to treat disease, and therefore Emerson cannot be "prior art" within the meaning of 35 U.S.C. §102.

The Examiner purports that Emerson or Greenberger, in combination with any one of Caplan, Schinstine, and Mardon, renders Applicants' invention obvious. In the Examiner's view, the secondary references Caplan, Schinstine, and Mardon all disclose the availability of microcarriers, diffusion chambers, and microcapsules as delivery methods for bone marrow stromal cells. Applicants contend that because none of the secondary references

corrects the deficiencies of Emerson, the Examiner has not met his burden of proving a prima facie case of obviousness.

One of the deficiencies in Emerson is that the reference does not teach Applicants' cells. Neither Caplan, Schinstine, nor Mardon overcomes that deficiency. Caplan discloses methods of adhering cells to a container, which is then implanted into defective skeletal tissue, for example, so that the cells can proliferate into bone tissue. Applicants submit that the cells in Caplan are not genetically altered in any way. In addition, in some aspects of the invention in Caplan, the cells are ultimately induced to differentiate into bone-forming cells within the diffusion chamber or the ceramic graft. Applicants' cells serve to continuously provide a protein to the host animal.

Further, Applicants contend that Caplan teaches away from the present invention in at least one aspect. In Caplan, diffusion chambers containing mesenchymal cells, which cells were physically isolated from the immune cells of the host animal were compared with porous ceramic carriers grafted with mesenchymal cells, which cells were not physically isolated from the immune cells of the host animal, in their ability to produce bone or cartilage (see column 12, line 57-column 13, line 5 and column 13, line 43-60). The data in Caplan indicated that bone/cartilage formation was not observed in any experiment using the diffusion chamber. Bone formation was observed and reproduced using the ceramic graft carrier (see column 13, lines 6-30). Therefore, Applicants contend that results demonstrating lack of bone production from the cells which are isolated from the cells from the host animal's immune system teach away from the present invention.

Applicants note that claim 69 of the present application requires the limitation that bone marrow stromal cells in the container be isolated from the cells of the host animal's immune system. The data in Caplan support the contrary to limitation. The cells that were <u>not</u> isolated from the host animal's immune system (i.e., on the ceramic graft) produce bone; the cells that were isolated did not produce bone. Therefore, one of skill in the art would not be motivated to isolate cells from the host animal's immune system (i.e., in the diffusion chamber), because they do not serve their intended purpose which, in Caplan, is to produce bone.

For these reasons, Applicants submit that Caplan, combined with Emerson, does not offer a prima facie case of obviousness. Applicants request reconsideration and withdrawal of the rejection with respect to the combination of Emerson and Caplan.

The Mardon reference also does not correct the deficiency in Emerson. Mardon does not teach or suggest the cells of Applicants' invention. Rather, Mardon teaches placing a mixture of marrow cells in a diffusion chamber for implantation in an animal (see page 158). The cells in the present invention are isolated by a method similar to the method used in Mardon, but with the additional step of culturing the cells for a period of time and discarding those cells which do not adhere to the culture dish (see for example, paragraph bridging page 36 and 37 of the present specification).

Further, the cells in Mardon are not genetically altered in any way. The cells in Mardon are a mixture of adherent and nonadherent cells isolated from the bone marrow of rats. The purpose of the experiment in Mardon was to determine whether that mixture of cells had any osteogenic potential when implanted within a diffusion chamber into a rat. There is no suggestion in Mardon that the mixture of bone marrow cells used in the experiments could be genetically altered and implanted to provide a protein to a rat or any other animal in need of the protein.

Since Mardon does not correct the deficiency in Emerson to define Applicants' cells, and further, does not teach or suggest use of a diffusion chamber in conjunction with Applicants' cells, Applicants request reconsideration and withdrawal of the rejection of the claims based on the combination of Emerson and Mardon.

Applicants are still unclear as to the relevance of the Schinstine reference as it pertains to the present invention. First, Schinstine does not overcome the deficiency of Emerson to teach the cells of Applicants' invention. Further, Schinstine also does not teach or suggest use of a container containing bone marrow stromal cells, which cells are physically isolated from the immune cells of the animal in which the container is implanted, to provide a protein to an animal in need of the protein.

Second, while Schinstine discusses use of microcarriers previously known in the art in order to enhance or inhibit cell proliferation, the microcarriers disclosed in Schinstine do not physically isolate the cells adhered to the microcarrier from the host animal's immune system. Without more, this reference cannot contribute to a prima facie case of obviousness.

None of Caplan, Mardon, or Schinstine overcomes the deficiency in Emerson to teach or suggest Applicants' cells. Further, neither of Caplan, Mardon, or Schinstine supports the claim language of claim 69, in which the container physically isolates the bone marrow

stromal cells of the present invention from the host animal's immune system. For all of these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 69-71, 77, 99-108, and 112 under 35 U.S.C. §103(a).

The Examiner has also rejected claims 69 and 77 under §103(a) in view of any of the combinations of references discussed above, and further in view of Flier and Beresford. The Examiner argues that there is a high likelihood of success that transfection of stromal cells with the vector comprising obesity factor DNA would be successful. Applicants point out here again that the Examiner is using the teachings in Flier and Beresford, which demonstrate success with gene therapy methods, to support an argument of obviousness. Applicants remind the Examiner, as described above, that references used to support a contention of obviousness must be enabling.

Applicants point out that the Examiner's rejections in the present Office Action are inconsistent with the Examiner's arguments to support the rejections. The Examiner rendered a rejection under 35 U.S.C. §112, first paragraph, to claims apparently directed toward gene therapy (claims 109-111); but then the Examiner, in supporting a 103(a) rejection, uses the Greenberger, Emerson, Beresford, and Flier references, which clearly indicate use of gene therapy techniques, Therefore, either the Examiner agrees that gene therapy is enabling since he has supported his obviousness rejection with the Greenberger, Emerson, Beresford, and Flier references, or the Emerson, Beresford, and Flier references must not be enabling for gene therapy in order to be in agreement with the Examiner's prior §112 argument that the art of gene therapy is unpredictable and not enabled. Applicants remind the Examiner of the argument presented herein that Emerson is not an enabling reference for the proposition for which it was cited. In any event, the 112 and 103 rejections are inconsistent with each other, and one must be withdrawn, because the Examiner simply cannot have it both ways.

However, even if the Examiner's argument did not rest on a premise in an art that he believes to be unpredictable, Applicants assert that neither Beresford nor Flier can correct the deficiencies of Greenberger, Emerson, Caplan, Mardon, or Schinstine. As discussed above, none of the references teaches Applicants' cells. Further, neither Caplan, Mardon, nor Schinstine, teach a container which physically isolates the Applicants' cells contained therein from the host animal's immune cells. Neither Beresford nor Flier teach or suggest Applicants' cells or a container which isolates Applicants' cells from immune cells of the host animal.

Applicants respectfully submit that combining Greenberger or Emerson with any one of Caplan, Schinstine, or Mardon, and further with Flier and Beresford, does not correct the deficiencies of Greenberger or Emerson because none of these references combined with either Greenberger or Emerson teaches all elements of the present invention.

In sum, Greenberger or Emerson combined with any of the above references does not render the invention obvious. In addition, Applicants request that the obviousness rejection be reconsidered and withdrawn in view of the foregoing arguments.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has either been overcome or is now inapplicable, and that each of the claims 69-71 and 77-, 97-108, 112, and 113 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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